REGULATION OF OPIOID PEPTIDE GENE EXPRESSION BY NICOTINE

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In the present study, the effects of nicotine administration on the levels of mRNAs coding for the three opioid peptide precursors (proopiomelanocortin (POMC), proenkephalin (PENK) and prodynorphin (PDYN)) in various rat tissues were investigated.
Various modes of nicotine applications were tested: One group of rats was acutely treated with two high doses of nicotine (0.5 mg/kg) and killed one day later. These animals showed a slight decrease in the levels of POMC mRNA in the intermediate lobe of the pituitary, but no change in anterior lobe of the pituitary and in the hypothalamus. PENK mRNA levels in various brain structures (hypothalamus, striatum, hippocampus) were essentially unaffected. However, a dramatic increase in the PENK mRNA levels was found in the adrenal medulla. PDYN mRNA levels in the striatum and hippocampus remained unchanged. A marked increase, in the PDYN mRNA levels, however, was seen in the hypothalamus. This increase was associated with an increase in the levels of mRNA coding for provasopressin.
Similar changes in the opioid peptide mRNA levels were obtained when rats were chronically infused with nicotine via osmotic minipumps (4 -10 mg/kg/s.c.) for 4 days. These changes became much less pronounced after 7 days tonic nicotine infusion and disappeared completely when the rat were tonically treated with nicotine for 2 weeks. This indicates the development of tolerance to these effects of nicotine. Interestingly, the mRNA levels coding for the α_3-subunit of the neural nicotinic receptors in the hypothalamus and the adrenal medulla remained unchanged suggesting that the tolerance to nicotine is not reflected by biosynthetic alterations of this particular nicotinic receptor subunit. On the other hand the development of tolerance appears to depend on the mode of nicotine administration. Thus, chronic application of nicotine (10 mg/kg/d) in a pulsatile fashion via minipumps (3 to 4 pulses/day) for 1 weeks still resulted in dramatic increases in the levels of PENK mRNA in the adrenal medulla.

The mechanism of the induction of PENK gene expression was studied in bovine adrenal medullary chromaffin cells in culture. Incubation of the cells with nicotine (10^{-6} M) resulted in a time-dependent up to 5 fold increase in PENK mRNA levels. After an initial lag phase (with no major alterations) PENK mRNA was markedly increased between 6 to 12 hours followed by a slower, steady increase up to 48 hours. The nicotinic antagonist tubocurarine (4×10^{-7} M), the Ca^{2+}-channel blocker D 600 (10^{-5} M) and the protein synthesis inhibitor cycloheximide (10^{-5} M) prevented the rise of PENK mRNA when given within the lag phase (0 to 4 hours after nicotine). This indicates that continuous entry of Ca^{2+}-ions and de novo synthesis of protein-like transcription factors are required for the activation of PENK gene expression by nicotine.

In conclusion, our results provide evidence that the administration of nicotine into rats results in specific alterations in opioid peptide gene expression. A particularly high increase in PENK mRNA levels was found in the adrenal medulla. Tonic application of nicotine for 1 to 2 weeks resulted in the development of tolerance to these effects. This tolerance development was not associated with any alterations in the gene expression of the α_3- subunit of neural nicotinic receptors. The development of tolerance to nicotine was not evident, when the drug was chronically applied in a pulsatile fashion. As revealed by in vitro experiments with bovine chromaffin cells, the induction of PENK gene expression by nicotine involves continuous influx of Ca^{2+}-ions and de novo synthesis of protein-like transcription factors.

Source: https://www.industrydocuments.ucsf.edu/docs/ntpk0000